Better results with cyanocuprol are usually obtained in patients previously treated with tuberculotoxoidin.

SUMMARY. 1. Cyanocuprol is very effective in all cases of the first stage. In the majority of cases of the second stage it is also effective. With patients of the third stage it many manifest its effect to a certain extent if favorable cases. are selected and proper dosage is given.

2. The effect of cyanocuprol cannot be called strictly chemotherapeutic. It shows in some respects a strong resemblance to tuberculin.

3. The essentials of the treatment with cyanocuprol lie in finding the proper dosage for each patient. If the individualization, which is especially important with this remedy, is properly carried out its value is indeed remarkable, surpassing all other remedies ever tried.

4. The combination of calcium prevents violent reactions and does not affect the efficacy of the drug.

5. The combination of immune therapy and sanatorium treatment is necessary.

6. The question of the duration of the treatment is an important one. According to our own experience if the patient is not improved after two or three injections, or is weakened, the dosage should be reduced or the interval extended. If this brings no improvement the treatement must be given up. Even in favorable cases, when the results are good after each injection, the treatment is best interrupted between the fifth and sixth and eleventh and twelfth injections, for at these times the condition is most improved. If treatment is continued in such cases there will be no benefit from it; instead there may be a return of previous symptoms and the patient's condition may become hopeless.

In conclusion, it is our pleasant duty to pay our best respects to Dr. Koga, and also to express our hearty thanks to Doctors Takagi, Imai, Yukawa, Honda, and Yano for their kind assistance throughout the whole period of our observations.

VAGINAL METASTASES OF HYPERNEPHROMA.

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THE urinary and genital apparatus in the female are closely connected both topographically and developmentally. In disease this intimate relationship becomes even more apparent. I need but mention the frequent occurrence of pyelitis in pregnancy, the effect upon the bladder of an incarcerated retroflexion of the gravid uterus, the role of cystocele in the etiology of genital prolapse, the relations of the ureters to cancer of the cervix uteri, the question of vesical fistulæ, etc.

The case recorded below is an additional contribution to the borderland between gynecology and urology:

Mrs. Z., aged fifty-four years, referred by Dr. F. R. Fry, complained of severe and persistent pain in the abdomen due to the presence, in the left hypochondrium, of a large, hard and immovable tumor supposed to be retroperitoneal. She had lost thirty pounds in weight within the last few months. Her appetite was poor; the bowels were constipated. There had never been an attack of hematuria or of vesical disturbance.

An irritating and slightly offensive discharge from the vagina, brownish in color and doubly suspicious in a woman past the menopause, called for a vaginal examination. The exploring finger touched two round protuberances springing from the anterior vaginal wall immediately behind the introitus. One of these lay in the median line and the other directly behind it and a little to the right. The elevations were of the size and shape of raspberries, soft in consistency and connected with the vaginal wall by a broad base. Both were easily shelled out with the finger-nail, which procedure left a shallow and but slightly bleeding depression behind. The color of the small growths was grayish red. The rest of the genital system presented no abnormalities; the uterus and ovaries were in a state of physiological atrophy.

The microscopic examination (Dr. G. McConnell*) of the small growths revealed unexpected and highly interesting conditions. In one of them the stroma was made up of a basal layer of connective tissue (Fig. 1). From this sprang a freely anastomosing network of delicate connective-tissue fibers carrying capillaries (Fig. 2). In the peripheral portion such connective-tissue fibers could not be distinguished and the stroma was altogether formed of capillaries which, near the surface, were seen distended with blood. The anastomosing bloodvessels formed distinct alveoli, and these alveoli were densely filled with large polygonal and round cells whose nuclei were well stained. While the contours of the cells were well marked the protoplasm had not taken the stain. In many of the cells there were one or more vacuoles (fat droplets?) while in others a granular arrangement was discernible in the cell body. In some of the cells the nucleus was pushed to one side (Fig. 3). In the periphery of the growth there were several places of hemorrhagic infarct with necrosis of the tissue. In the deeper layers, near the basal connective-tissue wall, there was a reticulum of connective-tissue fibers within which small nests of the same polygonal cells were confined. Deposits of pigment were altogether absent.

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* It is a pleasant obligation to thank Dr. McConnell, now in Waterloo, Iowa, for his valuable help.

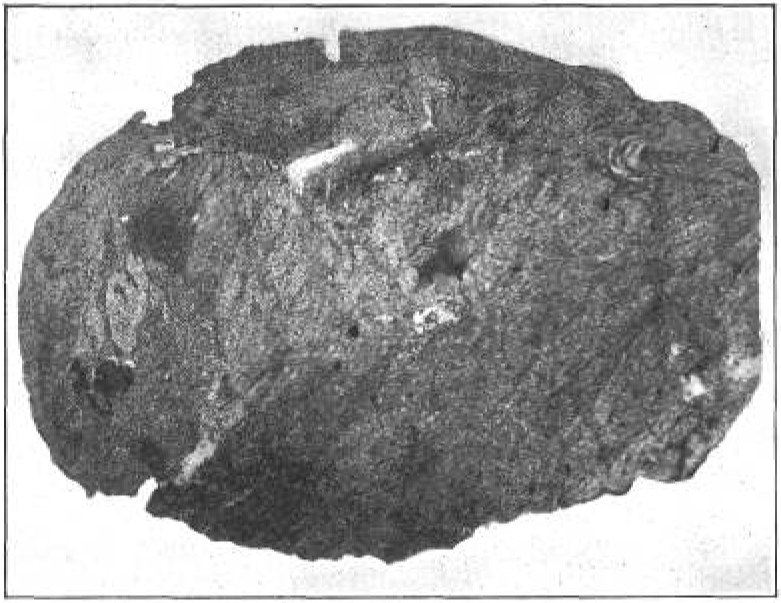

FIG. 1.—Vaginal metastasis. A freely anastomosing network of delicate connective-tissue fibers forms alveoli which are filled with cells. Note the light color of the alveoli. Bausch & Lomb, 32 mm. Tessar.

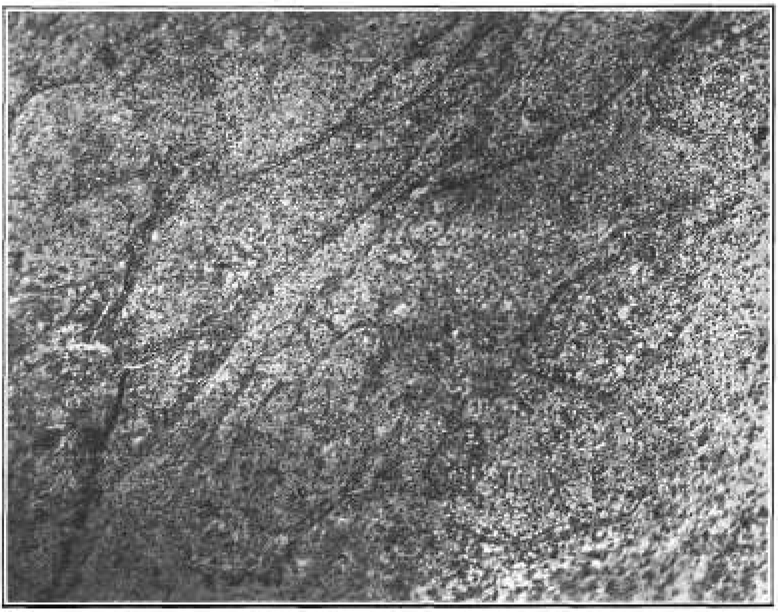

FIG. 2.—Alveoli in Fig. 1. enlarged. The connective-tissue septa carry capillaries. Bausch & Lomb, 16 mm. obj. 5 x ocul.

The microscopic picture of the second vaginal growth was somewhat different. The base was made up of a broad band of blood cells without any connective tissue. The contour of the tumor was round, with the exception of one indentation, and was, for the most part, covered with a very thin layer of epithelial cells derived, in all probability, from the mucous membrane of the vagina, and spread out over it like a decidua reflexa (Fig. 4). The stroma was formed by an excessively large number of tortuous and greatly engorged bloodvessels. The endothelial lining of these was plainly visible, but other constituents of the vessel walls were absent; connective tissue was discernible in the picture only in faint traces. The parenchyma between the bloodvessels was formed by the same large polygonal cells seen in the other growth. In certain places these cells formed solid columns. Vacuoles and granular arrangement within the cell bodies were also present, but neither pigment nor giant cells could be found. Extravasation of blood had occurred in a few places near the periphery. Round-cell infiltration was observed in two small areas beneath the vaginal covering.

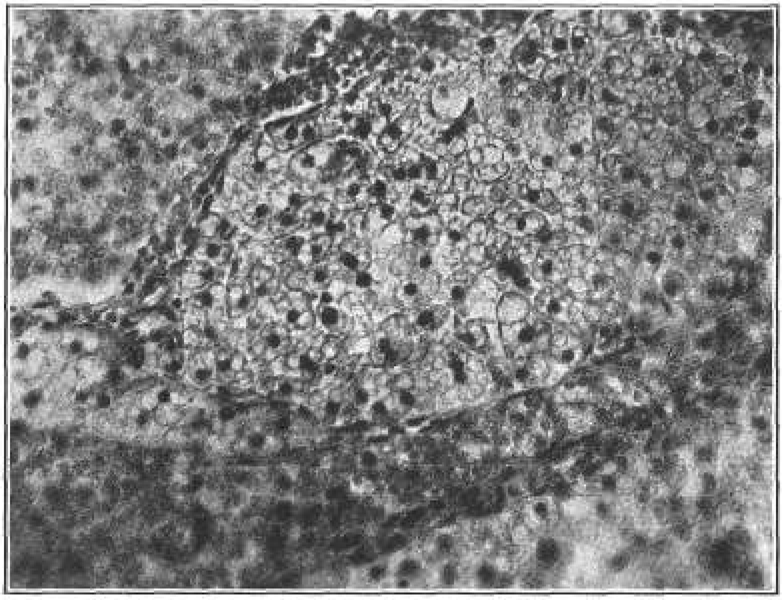

FIG. 3.—In the peripheral portion the alveoli are formed by capillaries. The alveoli are packed with large polygonal and round cells whose nuclei are well stained while the protoplasm has not taken the stain. Many of the cells are arranged in rows and are directly continuous with the endothelium of the bloodvessels without any intervening connective tissue. Note the vacuoles and eccentrically located cell nuclei. Bausch & Lomb, 4 mm. obj. 5 x ocul.

While, thus, in the first picture the alveolar arrangement of the large polygonal cells predominated, the angiomatous condition of the bloodvessels was more conspicuous in the second growth. Both pictures, however, had so many features in common that they had to be considered as various types of one and the same condition.

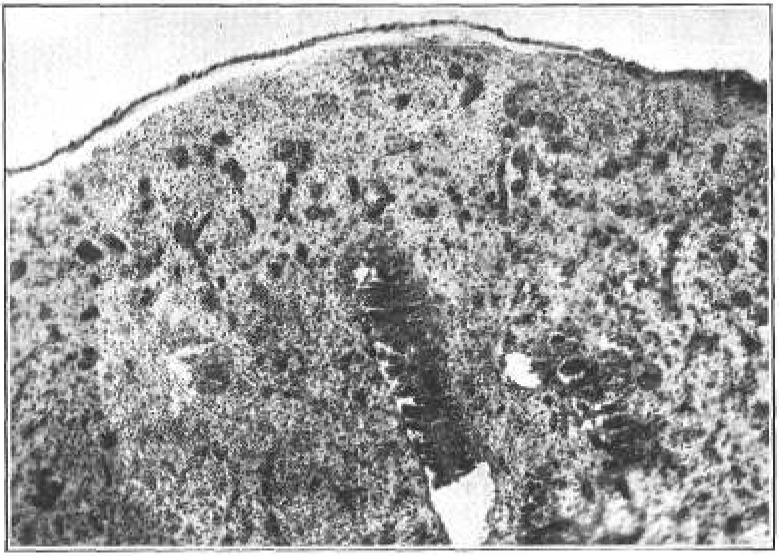

FIG. 4.—Periphery of second vaginal growth. The thin covering is derived from the vaginal mucosa. Note the abundance of tortuous and engorged bloodvessels and the light color of the parenchyma cells. Bausch & Lomb, 8 mm. obj. 5 x ocul.

Both tumors presented microscopically a peculiar glassy appearance, and from the resemblance of their structure to that of the adrenal glands they were interpreted as being hypernephromatous in nature and metastases of the large mass found previously in the left hypochondrium. This latter mass, therefore, was diagnosed as a hypernephroma of the kidney.

That this supposition was correct was proved at the sudden death of the patient three or four days after our diagnosis had been made. At the demand of the family, autopsy was restricted to the abdominal cavity and revealed the hypochondriac tumor to be a typical hypernephroma which had developed from the upper pole of the left kidney. The rest of the abdominal cavity was apparently free from metastases, and from our postmortem findings no definite cause of death could be determined. The two wounds in the vagina resulting from the enucleation of the metastatic growths had almost healed.

The kidney tumor had the size of a large man's fist.* Histologically, it presented the characteristic features of hypernephroma identical with those found in the vaginal growths. In addition, however, there were also papillary structures in which rows of polygonal cells were arranged along almost invisible capillaries, which in turn branched out from a central bloodvessel of a larger caliber. In several places these rows of cells, two or three deep, had a lumen in the center, caused perhaps by necrosis, thus forming a pseudoglandular arrangement. These gland-like structures were, however, easily distinguished from true glandular spaces which could be observed at about the middle of the microscopic field and were separated from the rest of the tumor by a capsule of connective tissue. We may assume that these glands belonged to the kidney proper and represented urinary tubules.

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* The tumor was exhibited at the International Surgical Congress in Brussels, but was lost on the way home.

EPICRISIS. Vaginal metastases of hypernephroma seem to be extremely rare. I have been able to find only the following nine instances of this sort in the literature at my disposal.

1. F. Henke[1] reports the case of a woman, aged sixty years, with multiple tumors of the vagina, which, at first, were thought to be metastases of uterine cancer. Besides, she had a pedunculated tumor of the skin of about the size of a goose egg and the shape of a mushroom. Postmortem revealed the presence of a typical malignant hypernephroma of the left kidney. This latter tumor as well as the growths in the skin and vagina contained a large amount of glycogen and presented identically the same microscopic picture. The cutaneous and vaginal tumors must therefore be considered as metastases of the suprarenal tumor.

2. A. von Rosthorn[2] demonstrated a vaginal metastasis of an "hemendothelioma" of the kidney. I was unable to find the original report. The name hemendothelioma, however, suggests that von Rosthorn presented his case at a time when the histogenesis of these tumors was still under discussion. Driessen,[3] Hildenbrand[4] and others believed that they originated from the endothelium of bloodvessels and lymphatics. As we shall see later the term "hypernephroma" has now been generally accepted, and Kelly[5] expressly states that this term includes the "endothelioma" of Driessen as well as the "angiosarcoma" of De Paoli, Beneke and Sudeck.

The case of von Rosthorn, however, is rather doubtful. Schottlaender[30] quite recently classified this case among those of "ectopic chorio-epithelioma."

3. Peham[6] speaks of a woman, aged fifty-nine years, who, for a few months, had complained of a bloody vaginal discharge; one and one-half years previously she had some urinary discomfort, and once there was an attack of hematuria. On examination a large hypernephroma of the left kidney was found. The anterior vaginal wall was infiltrated and a sessile growth the size of a hazelnut was discovered directly behind the introitus. The structure of this growth, on microscopic examination, was identical with that of the hypernephroma.

4. R. Freund[7] reports a vaginal metastasis in a woman, aged fifty-six years, which had appeared one and one-half years after the extirpation of the left kidney for "sarcoma." The metastatic growth had the size of a cherry; it was located upon the anterior vaginal wall to the left of the urethra, and had caused hemorrhages for the past six months. The microscopic examination of both the primary and metastatic tumors revealed typical hypernephroma.

5. Hoffmann[8] found in a woman, aged sixty-one years, a cauliflower growth in the vagina as a metastasis of a hypernephroma of the left kidney. There were numerous other metastases throughout the body.

6. Alban Doran[9] described in detail the findings in a woman, aged forty years, whose right kidney was extirpated for hypernephroma. Aside from metastases in the liver and lungs, there were several metastatic growths, both sessile and pedunculated, within the vagina.

7. In the discussion following Doran's paper, Overy[34] described a similar case in which a polypoid mass had been found attached to the anterior vaginal wall. This was removed and a large tumor in the right side of the abdomen was discovered. Two months later the vaginal growth had recurred and it was again removed. The patient died a month later. The postmortem examination showed that the abdominal tumor was primary and was a malignant adrenal tumor starting in an adrenal rest. There were numerous secondary deposits in the liver and lungs, sections of which showed more or less typical adrenal tissue.

8. Graefenberg[10] found, in a woman, aged fifty-four years, a tumor of the left kidney and two nodes of walnut and hazelnut size respectively upon the anterior and posterior vaginal walls immediately behind the introitus. Microscopic examination of these nodes revealed the picture of malignant hypernephroma. The vaginal growths obviously were metastases of the renal tumor.

9. Graefenberg[10] discovered, in a woman, aged sixty-five years, a deeply pigmented tumor of the vulva in the vicinity of the meatus urinarius. Microscopically the tumor showed the characteristics of hypernephroma, and upon autopsy, a malignant hypernephroma of the left kidney the size of a child's head was found. The growth in the vulva was the only metastasis of the renal tumor.

An interesting feature of my own case is the fact that the microscopic examination of the vaginal metastases enabled us to correctly diagnose the primary tumor. In like manner did Graefenberg[10] diagnosticate both his cases of hypernephroma from a histological examination of the secondary manifestations. Indeed, it is often only the metastasis which causes the patient to seek medical aid while the primary tumor, for the time being, produces no symptoms at all. Thus Hoffmann[11] found in a man who entered the hospital, because of pain in his leg, a metastasis in the femur which led him to search for and find a hypernephroma of the kidney; and Israel[12] and Albrecht[13] likewise observed bone tumors which, after careful observation, were recognized as metastases of a hitherto obscure hypernephroma.

In my case the vaginal tumors, which from their proximity, may be considered as one, were clinically the only metastasis in the body; but as the autopsy had to be limited to the abdominal cavity the possibility of other metastases in the brain or thoracic cavity cannot definitely be excluded. Contrary to the opinion of Berg[31] there are but very few instances of solitary metastases of hypernephroma in literature. The case of Graefenberg[10] has already been referred to. In one of Albrecht's cases[13] a metastasis in the scapula was the only one in the body.

As a rule, however, hypernephroma causes multiple metastases. They are most frequently found in the bones and lungs, but since the disease is disseminated by way of the bloodvessels, almost all organs may become affected. Hoffmann[8] describes hypernephroma metastases in brain, liver, lungs, kidney, bronchial glands, various bones, the skin of the thigh and the vagina. Funccius[14] reports metastases in the ovary and pancreas, and Garceau[15] mentions, in addition, metastases in spleen, uterus, intestines, bladder and omentum. Harttung[33] recently recorded a metastasis in the spine.

In view of this multiplicity of metastasation in the various parts of the body the rarity of vaginal metastases is doubly remarkable. Graefenberg[10] endeavors to explain this phenomenon. He says that particles of the tumor usually enter the vena cava through the renal vein; thence they are carried through the heart into the pulmonary arteries. This, however, explains merely the frequency of metastasis in the lungs. According to Sutter's investigations, retrograde metastases of malignant kidney tumors may at times by disseminated throughout the entire genito-urinary apparatus by way of the vena spermatica. This possibility seems plausible in cases in which metastases are found in the ovaries, uterus and upper portions of the vagina for these localities are exposed to retrograde transportation of tumor particles by way of the spermatic vein through anastomoses with the plexus pampiniformis. This explanation, says Graefenberg, is, however, not sufficient for metastases in the lower portion of the vagina and the vulva. Tumor particles from the kidney can reach the vulva by way of the spermatic vein only if there is an anastomosis of the plexus pampiniformis with the obturator vein. Such an anastomosis exists at times. The obturator vein, again, receives rami pubici from the external genitals, and thus a direct communication from the renal vein to the vulva is established. Since the left spermatic vein empties into the left renal vein, such a retrograde transportation of tumor particles to the external genitals seems more likely on this side than on the other because, under ordinary circumstances, the right spermatic vein does not empty into the renal vein but directly into the vena cava.

Graefenberg's contentions are borne out by the studies of Kownatzki[16] on the distribution of veins in the female pelvis. Kawnatzki depicts in Fig. 4 an old parametritis which has led to an anastomosis between the plexus pampiniformis and the obturator vein. He furthermore shows in his dissections that even without such an anomaly the pubic veins carry blood from the external genitals directly into the so-called median iliac vein which by means of the uterine veins is connected with the spermatic vein and thus with the renal vein.

The theoretical explanation of Graefenberg is supported by the fact that of the 10 hypernephromata here collected, 7 were on the left side. In 1 case the location of the tumor was not stated. In the case of Doran the hypernephroma was situated on the right side; the metastases were in the upper portion of the vagina and therefore do not come within the scope of this particular consideration. In Overy's case the exact location of the metastasis is not given. The preponderance of hypernephroma on the left side in these cases does not seem accidental. Keyes[17] says that renal growths are about equally frequent on the two sides, and Garceau[15] states: "The right side is a little more frequently affected than the left; 82 cases are recorded in which the disease occurred on the right, 77 on the left and in 17 the side was not stated." In contradistinction to these statistics, among which there are a number of individual observations, I find that the proportion is reversed if we consider whole series of cases reported by one and the same author, as in the following table:

Author.	Right.	Left.	Not stated.	Total.
Israel[12]	7	10	0	17
Kelly[5]	1	4	1	6
Albrecht[13]	9	19	0	28
Scudder[18]	2	3	1	6
	19	36	2	57

The diagnosis of hypernephromatous metastases in the vagina rests upon the microscopic examination. These metastases reproduce exactly in their minute structure the characteristics of the parent tumor (Garceau), and the latter, again, suggests histologically the structure of the cortex of the adrenal. It will be remembered that the adrenal gland is composed of a medullary and a cortical portion. The latter is subdivided into three more or less distinct layers, the *zona glomerulosa, zona fasciculata* and *zona reticularis.* In the case of tumor formation, however, these three layers are not evenly represented; the fascicular layer usually predominates. Moreover, as the tumor grows, atypical formation can occur, which may resemble adenoma, sarcoma, endothelioma, or carcinoma.[32] This variability of the microscopic picture has been the cause of much confusion until Lubarsch[19] and Birch-Hirschfeld[20] suggested that an indifferent name should be chosen which would leave the question of histogenesis in abeyance and would merely signify that these tumors were derived from the adrenal. The name "hypernephroma" proposed by them has now been almost generally accepted.

That these tumors were of adrenal origin was first shown by Grawitz[21] in 1883, who, moreover, proved that the tumor formation did not so much take place in the adrenal proper as in "aberrant" adrenal tissue, which is so frequently found in the kidney. Such aberrant adrenal tissue was later demonstrated in all parts of the abdomen, but particularly in the urogenital tract, by Imbert, Schmorl,[22] Marchand, Chiari, Hanau, Ulrich, Targett,[23] Aichel,[24] Pick,[25] and numerous others. Consequently, primary hypernephromata originating from these so-called adrenal rests have been observed in organs other than the kidneys. Thus, Keen, Pfahler and Ellis,[26] in a collection of 163 cases, found 157 in the kidney, 3 in the adrenal, 2 in the liver and 1 in the uterus. Pick[24] and Bovin[27] described primary hypernephroma in the ovary and Weiss[28] a like tumor in the broad ligament.

Although usually of slow growth, hypernephroma is potentially a malignant tumor, and metastasation will occur sooner or later. These metastases are almost always multiple, as mentioned above, and their presence contra-indicates any operation.

To return now to vaginal metastases with which we are here more particularly concerned, they are of considerable practical importance to the gynecologist. As Freund[7] justly points out, metrorrhagias or a bloody vaginal discharge, after a previous nephrectomy, should make us think of metastases of hypernephroma, particularly if the anterior vaginal wall near the introitus is affected.

Malignant tumors of the vagina are usually considered primary. It seems but reasonable to think that in some such cases the tumor is in reality a metastasis (Veit[29]). If more attention would be given to this point in future the bad prognosis of malignant new growth of the vagina would, to a certain extent at least, be explained. It is not at all illogical to surmise that many a supposed sarcoma or carcinoma of the vagina will, on careful microscopic examination, prove to be hypernephromatous in nature and that a thorough investigation will lead to the discovery of the tumor in the kidney.

SUMMARY. In a woman, aged fifty-four years, a large retroperitoneal tumor on the left side was found whose nature could not be determined. Vaginal examination revealed the presence of two growths in the anterior vaginal wall near the introitus. These growths were of the size and shape of raspberries and were easily shelled out with the finger-nail. Microscopic examination showed typical hypernephroma. It was then assumed that the two vaginal growths were metastases of the obscure retroperitoneal tumor and that the latter was a hypernephroma of the kidney. The patient died suddenly a few days later and autopsy fully confirmed the correctness of the diagnosis.

Vaginal metastases of hypernephroma are extremely rare. Literature contains but 9 other instances of this kind. It is, however, probable that many cases of primary sarcoma of the vagina are in reality hypernephromatous in nature and secondary to a malignant tumor of the kidney.

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